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Bone "The Pathogenesis of Sepsis" Ann Int Med 115(6) 457-469 1991.
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REVIEW

The Pathogenesis of Sepsis

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■ Sepsis and its sequelae (sepsis syndrome and septic shock) are increasingly common and are still potentially lethal diagnoses. Many mediators of the pathogenesis of sepsis have recently been described. These include tumor necrosis factor α (TNFα), interleukins, platelet activating factor, leukotrienes, thromboxane A_2, and activators of the complement cascade. Neutrophil and platelet activation may also play a role. Other agents that may participate in the sepsis cascade include adhesion molecules, kinins, thrombin, myocardial depressant substance, β-endorphin, and heat shock proteins. Endothelium-derived relaxing factor and endothelin-1 are released from the endothelium and seem to exert a regulatory effect, counterbalancing each other.

A central mediator of sepsis does not seem to exist, although TNFα has been commonly proposed for this role. Animal studies are difficult to extrapolate to the clinical setting because of cross-species differences and variations in experimental design. Rather than being caused by any single pathogenic mechanism, it is more likely that sepsis is related to the state of activation of the target cell, the nearby presence of other mediators, and the ability of the target cell to release other mediators. Also important is the downregulation or negative feedback of these mediators or the generation of natural inflammation inhibitors, such as interleukin-4 and interleukin-8.

Endothelial damage in sepsis probably results from persistent and repetitive inflammatory insults. Eventually, these insults produce sufficient damage that downregulation can no longer occur; this leads to a state of metabolic anarchy in which the body can no longer control its own inflammatory response.

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Advances in medical practice and technology have increased the risk of sepsis and its sequelae (the sepsis syndrome and septic shock) (1-3). Among these are the aggressive use of catheters and other invasive equipment; implantation of prosthetic devices; and administration of chemotherapy to cancer patients or of corticosteroids and other immunosuppressive agents to patients with organ transplants or inflammatory diseases. In addition, improvements in medical care have given longer life spans to the elderly and to patients with metabolic, neoplastic, or immunodeficiency disorders—but these groups remain at increased risk for infection.

Hope is in sight, however. Discoveries made in the last few years have vastly increased our understanding of the pathogenesis of sepsis and its sequelae. Many of the mediators responsible for the endothelial derangements underlying these disorders have been identified. Even more important, these discoveries have led to a number of new therapies—treatments that hold promise of significantly reducing the high mortality associated with sepsis. Many of these new therapies are now under investigation and may soon be available for clinical use.

My purpose here is to summarize what we have learned about these new mediators and then to propose a new hypothesis for understanding how these mediators produce the endothelial dysfunction that is widely believed to be one of the key derangements underlying sepsis and its sequelae. In brief, I submit that these disorders result from panendothelial injury, caused by repetitive, localized foci of inflammation, which, in turn, produces an increase in capillary permeability. I do not mean to imply that endothelial damage is the sole cause of these disorders. Metabolic derangements, coagulative disorders, and myocardial depression undoubtedly also play a role. Only by recognizing that patients with sepsis, the sepsis syndrome, or septic shock have multiple local defects in endothelial permeability, however, can we begin to formulate effective treatment regimens.

Epidemiology

It is difficult to establish the true incidence of sepsis and its sequelae for two reasons. First, there has been a lack of consensus about the definition of these diseases. This problem is perhaps best illustrated by the fact that reports of mortality associated with septic shock range from 10% (4) to 90% (1). To overcome this problem, a framework for defining levels of infection from uncomplicated bacteremia through refractory septic shock has recently been proposed (5) and is presented in Table 1.

The second problem is that none of the disorders listed in Table 1 is a reportable disease. However, recent data from the Centers for Disease Control suggest

Table 1. A Uniform System for Defining the Spectrum of Disorders Associated with Sepsis*

Disorder	Requirements for Clinical Diagnosis
Bacteremia†	Positive blood cultures
Sepsis	Clinical evidence suggestive of infection *plus* signs of a systemic response to the infection (all of the following): Tachypnea (respiration > 20 breaths/min [if patient is mechanically ventilated, > 10 L/min]) Tachycardia (heart rate > 90 beats/min) Hyperthermia or hypothermia (core or rectal temperature > 38.4 °C [101 °F] or < 35.6 °C [96.1 °F])
The sepsis syndrome (may also be considered *incipient septic shock* in patients who later become hypotensive)	Clinical diagnosis of sepsis outlined above, *plus* evidence of altered organ perfusion (one or more of the following): Pao_2/Flo_2 no higher than 280 (in the absence of other pulmonary or cardiovascular disease) Lactate level above the upper limit of normal Oliguria (documented urine output < 0.5 mL/kg body weight for at least 1 hour in patients with catheters in place) Acute alteration in mental status Positive blood cultures are not required‡
Early septic shock	Clinical diagnosis of sepsis syndrome outlined above, *plus* hypotension (systolic blood pressure below 90 mm Hg or a 40 mm Hg decrease below baseline systolic blood pressure) that lasts for less than 1 hour and is responsive to conventional therapy (intravenous fluid administration or pharmacologic intervention)
Refractory septic shock	Clinical diagnosis of the sepsis syndrome outlined above, *plus* hypotension (systolic blood pressure below 90 mm Hg or a 40 mm Hg decrease below baseline systolic blood pressure) that lasts for more than 1 hour despite adequate volume resuscitation and that requires vasopressors or higher doses of dopamine (> 6 μg/kg per hour)

* Adapted from Reference 5.
† The related term *septicemia* is imprecise and should be abandoned.
‡ The sepsis syndrome may result from infection with gram-positive or gram-negative bacteria, pathogenic viruses, fungi, or rickettsia; however, an identical physiologic response may result from such noninfectious processes as severe trauma or pancreatitis. Blood cultures may or may not be positive.

that the incidence of septicemia (which they define as systemic disease associated with the presence and persistence of pathogenic microorganisms or their toxins in the blood) increased 139% between 1979 and 1987, from 73.6 to 175.9 cases per 100 000 persons (3). Septicemia is now ranked as the thirteenth leading cause of death in the United States (3, 6) and is estimated to account for $5 to $10 billion of American's annual health care expenditures (3).

The frequency with which shock develops in patients with sepsis varies. Martin and coworkers (2) found a 17% incidence of shock in patients with coagulase-negative staphylococcal infection. In contrast, shock developed in 47% of the bacteremic patients and 30% of the nonbacteremic patients in the placebo group of the Methylprednisolone Severe Sepsis Study (7). Overall estimates suggest that shock develops in about 40% of patients with sepsis (8).

The onset of sepsis—particularly septic shock—portends a poor prognosis. In a study of 487 patients consecutively admitted to a medical intensive care unit, sepsis developed in 196 (40%) (9). Forty-four percent (86 of 196) of the septic patients died, but only 16% (45 of 291) of the patients without sepsis died. Other studies have estimated that the mortality associated with sepsis ranges from about 10% to 20% (10) up to 50% (11, 12). (As noted above, variations in definition may account for at least some of the variations in mortality rates.) The onset of shock may increase mortality to as high as 77% (13) or 90% (1). In our studies, the sepsis syndrome without shock had a mortality of 13%, the sepsis syndrome presenting with shock had a mortality of 28%, and shock developing after the sepsis syndrome had a mortality of 43% (7).

Pathophysiology

The definitions presented in Table 1 are useful clinically and experimentally, because they allow us to identify patients and to assess the outcome of treatment in a uniform fashion. Nevertheless, sepsis, the sepsis syndrome, and septic shock are not discrete entities; rather, these terms delineate increasingly severe stages of the same disease and result from the same pathophysiologic processes. For simplicity's sake, I will use the term "sepsis" in much of the remainder of this article to denote all three disorders. I will ultimately explain, however, how these pathophysiologic processes contribute to the different stages of disease severity.

The mediators of sepsis that are most likely to produce endothelial dysfunction are listed in the Appendix. Also included in the Appendix are the effects of these mediators that are most likely to contribute to the development of sepsis.

As detailed as this Appendix may seem, several limitations should be noted. First, many of the mediators of sepsis probably remain undiscovered. Second, our knowledge of the mediators that have been discovered

is far fr m complete, but we do know that many of these mediators exert effects that may be protective of the host in one setting but injuri us in nother (14, 15). Third, these mediators interact in a very complex manner; although interactions are often synergistic, at times they may be quite antagonistic. Although still incompletely underst od, this nexus can be seen as a cascade that is initiated by a focus of infection or injury and ends with severe endothelial damage, profound hemodynamic derangements and, often, death.

The initiating event in this "sepsis cascade" is the release of endotoxin or a comparable substance into the circulation (Figure 1). (I use endotoxin in this discussion because gram-negative bacteria are frequently the cause of sepsis and because much of the work that has been done to elucidate these mediators was done using endotoxin.) Enterotoxin, toxic shock syndrome toxin-1, gram-positive or yeast cell-wall products, and viral or fungal antigens, however, can also initiate the sepsis cascade (16, 17). Noninfectious stimuli can also produce an identical physiologic response. Whether this response can truly be called "sepsis," however, has been debated.

Once in the circulation, endotoxin prompts the release of tumor necrosis factor α (TNFα), interleukin 1, interleukin-6, interleukin-8, and platelet-activating factor (PAF) from mononuclear phagocytes and other cells, including the endothelial cells themselves (18-21). The coagulation cascade and complement system become activated, although it is not clear whether this is a direct result of endotoxin (12, 22), stimulation by TNFα (23-26), or another mediator (27-30), or both.

After release of TNFα, interleukin-1, and PAF, arachidonic acid is metabolized to form leukotrienes, thromboxane A_2, and prostaglandins (especially prostaglandin E_2 [PGE_2] and prostaglandin I_2 [PGI_2]) (31). Interleukin-1 and interleukin-6 activate the T cells to produce interferon-γ, interleukin-2, interleukin-4, and granulocyte-monocyte colony-stimulating factor (14, 32-34).

Almost all of these agents have direct effects on the vascular endothelium. Endotoxin (16), TNFα (16, 35), PAF (36), leukotrienes (37), and thromboxane A_2 (31) each increase endothelial permeability. The vascular endothelium also seems to be the primary target for interleukin-1-induced changes in sepsis (14).

The endothelium, in turn, releases two additional substances, endothelium-derived relaxing factor (EDRF) (38, 39) and endothelin-1 (39, 40). These two substances seem to counterbalance each other; EDRF relaxes smooth muscle and inhibits platelet aggregation (41), whereas endothelin-1 is a potent vasoconstrictor (40).

Activation of the complement cascade (particularly fragments C3a and C5a [42]) results in vascular abnormalities (43-45) and neutrophil activation (46, 47). Neutrophils may also be activated directly by most of the mediators listed above (28, 26, 29, 31, 48-50). As a result, neutrophil-induced damage may occur during degranulation (through release of free radical oxygen species and lysosomal enzymes), during aggregati n (through microemboli formation), and during adherence to the endothelium (through vasodilation) (14, 47).

Platelets may also be involved in the sepsis cascade, although the evidence for this is less clear. They may damage the endothelium in two ways: by inducing vasoconstriction and by neutrophil stimulation (51). A derivative of platelets, transf rming growth fact r β_1, may also be involved (52).

Other agents that may be part f the sepsis cascade include adhesion molecules (53), kinins (54-56), thrombin (57-59), myocardial depressant substance (60-62), beta-endorphin (63, 64), and heat shock protein (65). Adhesion molecules and thr mbin may help promote endothelial damage; interleukin-4, interleukin-8, and heat shock protein may protect against it. It is not yet clear, however, exactly how these agents are activated or what specific role they play.

A Central Mediator of Sepsis?

As complicated as this cascade may seem, it may actually oversimplify the clinical picture. Because most of these mediators can prompt release of the others (and, in at least some cases, of themselves), it is often difficult to ascribe a given effect to a specific mediator. Further, it has recently been found that many of these mediators have different effects in combination than they have individually (66). It has thus been extraordinarily difficult to find the mediator (or mediators) that is most directly responsible for sepsis, but it has been hoped that the discovery of such a central mediator would permit development of more effective treatment regimens.

Toward this goal, a great deal of attention has recently focused on the role of TNFα. The arguments put forth for why this mediator should be considered central can be summarized as follows:

1. Tumor necrosis factor α levels are often elevated in a variety of septic states (67-76).

2. Many of the invasive stimuli known to cause sepsis, such as endotoxin and enterotoxin, prompt macrophages to release TNFα (16).

3. Injection of a lethal dose of endotoxin causes a sharp rise in TNFα levels in animals (77); injection of sublethal doses causes a smaller, but still marked, increase in TNFα levels in healthy human volunteers (76, 77-79).

4. Administration of large doses of TNFα duplicates many of the signs and symptoms of septic shock, including hypotension, neutropenia, and increased edema and pulmonary permeability (35).

5. Administration of antibodies to TNFα protects against the lethal effects of subsequent endotoxin challenge (80-82).

Unfortunately, as elegant and as seemingly persuasive as this argument is, it has several flaws. First, as our knowledge of TNFα has increased, it has become clear that TNFα levels are elevated in a wide variety of conditions other than sepsis. From its earliest discovery, TNFα was known to lyse cancer cells (83), and many cancer patients have been found to have increased circulating TNFα levels (84, 85). Elevated TNFα levels are also associated with various arthritides, including rheumat id arthritis (86) and systemic lupus erythemat sus (87), and als with the acquired immunodeficiency syndrome (88), leprosy and leishmaniasis (89, 90), coal workers' pneumoconi sis (79), and

alcoholic hepatitis (91). Raised TNFα levels have also been found in patients with congestive heart failure (92). Thus, TNFα, at best, can be considered a nonspecific mediator of inflammation with additional noninflammatory roles. The TNFα levels found in patients with these other disorders are often not markedly different from those found in most patients with sepsis.

Further, many septic patients do not have elevated—or even detectable—TNFα levels (93, 70-72), and many healthy persons have measurable levels of TNFα (72-74). One study reported that mean TNFα levels in 124 normal persons was 75.3 ± 15.6 pg/mL (73). Consequently, it is difficult to determine exactly what should be considered a "normal" TNFα level. When we re-evaluate the studies of TNFα levels in septic patients in light of these data, it becomes more difficult to conclude that TNFα levels are increased sufficiently so that they can be considered responsible for most of the findings in sepsis.

Some investigators have argued that the phasic nature of TNFα release makes it difficult to detect elevated plasma levels (17). I believe that we must think of TNFα as a paracrine, not an endocrine, hormone (that is, it is a hormone that exerts predominantly local, rather than systemic, effects); high circulating levels of TNFα may never be present in many patients.

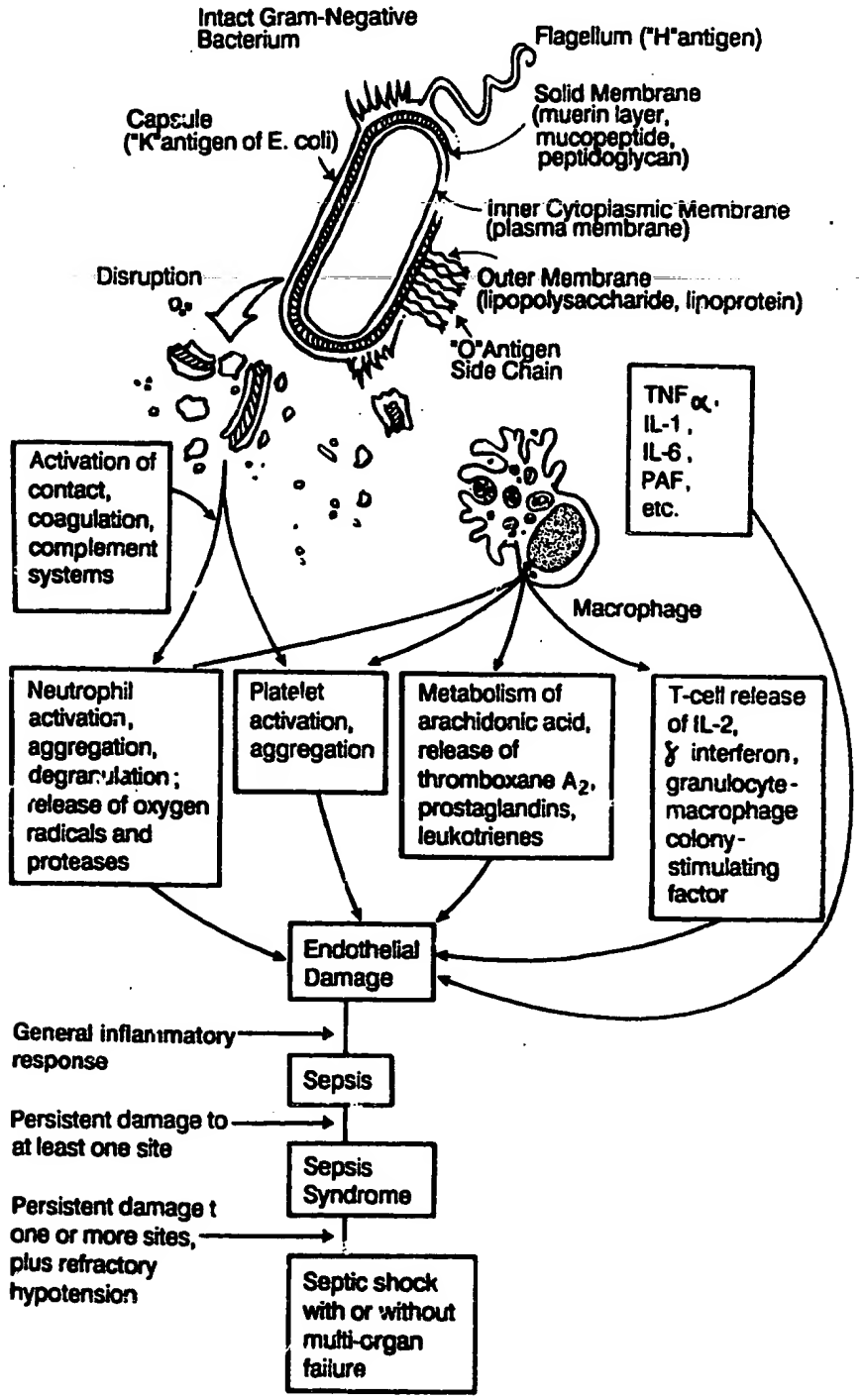

Figure 1. Schematic of sepsis. Note that although the schematic illustration somewhat oversimplifies the pathophysiologic process, it does provide a framework for understanding a complex chain of events. The pathways are not distinct, and the effects of any one mediator may vary with physiologic conditions. Massive endothelial damage does not ordinarily occur because there are many points at which feedback loops downregulate mediator release. If the body cannot restore homeostasis, however, the generalized inflammatory response will produce clinical evidence of sepsis. Persistent endothelial damage to at least one site will produce signs of organ failure (the sepsis syndrome); if hypotension develops and proves refractory to treatment, the patient will meet the criteria for septic shock.

Second, we must be careful when extrapolating the results of animal studies to the clinical setting. There are significant cross-species differenc ; in response to endotoxin and other mediators (94). Further, most cytokines are species-specific and thus administration of a human cytokine (or antibody to that cytokine) may not produce an accurate response in an animal model (95, 96). Differences in experimental techniques and methods of TNFα measurement cloud the picture still further.

We must also be cautious when interpreting the results of experiments in human volunteers. By definition, these volunteers are healthy, whereas patients with septic shock are severely ill, immunocompromised, or both, even before shock sets in. Additionally, such studies must use an artificial dose of endotoxin—one that is large enough to cause a measurable response but low enough not to cause death. This dose is generally administered as a single intravenous bolus, which is probably not comparable to the pattern of release in sepsis.

Third, administration of antibodies to endotoxin also protects against the lethal effects of subsequent endotoxin challenge, but in animal models it does not lower the rise in TNFα levels caused by endotoxin administration (97). Also, in mice infected with *Histoplasma capsulatum*, administration of antibodies to TNFα accelerates death (98).

Finally, TNFα is not the only mediator that can replicate the symptoms of sepsis. Administration of low doses of either interleukin-1 or PAF, for example, has been shown to induce a shocklike state (99-101). Unfortunately, many of the same arguments that can be made against TNFα as the central mediator of sepsis can also be made against interleukin-1 and PAF. Elevated levels of interleukin-1 can be found in patients with inflammatory bowel disease (102), systemic juvenile chronic arthritis (103), rheumatoid arthritis (104), and pulmonary fibrosis and sarcoidosis (105). Platelet-activating factor has been detected in patients with asthma (106) and kidney disease (107).

This is not to say that TNFα (or interleukin-1 or PAF) does not have a role in the pathogenesis of sepsis. It does. It may well be one of the most important mediators in the sepsis cascade, but its effects occur predominantly at a local level. High circulating titers of TNFα may portend poor prognosis for patients with septic shock (68, 69, 71, 75, 76), although this has been questioned by some (72). Too many patients with too many different disorders, however, have elevated TNFα levels without suffering circulatory collapse, and too many patients with sepsis have no or only low TNFα levels. High circulating levels of TNFα are thus not a prerequisite for the development of sepsis.

Mediator Interactions

If there seems to be no central mediator that explains the origins of sepsis, we must consider whether there is a specific interaction between two or more mediators that provides the prime impetus. The mediators in the sepsis cascade interact in various ways. Some interactions seem to augment the host response t infection. Interferon-γ and TNFα, for example, can enhance the phagocytic activity of neutrophils (26). Other interactions appear to limit inflammation, restore homeostasis, or both. The cycle in which TNFα prompts PGI_2 release (31) and then $^{D}GI_2$ suppresses further TNFα synthesis (108) is one example. Another is the process by which interleukin-8 decreases neutrophil adherence to the endothelium (109). Similarly, the products of the neutrophilic burst can inactivate leuk trienes at inflammatory sites (110). The vasodilatory effects of EDRF counterbalance the vasoconstrictive influence of endothelin-1 (39, 111).

The interactions of other mediators, however, seem more likely to disrupt homeostasis. For example, TNFα, interleukin-1, and PAF are able to promote release of one another—and their own continued release (112). Activation of T cells (mediated in large part by interleukin-1) causes release of interferon-γ; interferon-γ, in turn, stimulates macrophages to release more interleukin-1 (27). Both TNFα and PAF promote arachidonate metabolism, but arachidonate derivatives can then prompt TNFα and PAF release (31).

Further, each of the mediators of sepsis can be produced by a wide variety of cells in many different parts of the body. Both TNFα and interleukin-1, for example, can be released by macrophages, lymphocytes, natural killer cells, astrocytes and microglial cells, Kupffer cells, and endothelial cells (20, 21, 32, 99, 113, 114). Platelet-activating factor can be produced by macrophages, neutrophils, eosinophils, endothelial cells, and platelets (29, 115-117). As a consequence, the number of interactions between mediators may be close to the number of mediators squared.

It is precisely because of the complexity of this cascade that it has been difficult to elucidate exactly what effects can be ascribed to each mediator. Moreover, many mediators have synergistic effects. Interleukin-1 and TNFα act synergistically in disrupting pulmonary vascular endothelium (99). Endotoxin has been shown to potentiate the effects of TNFα (118).

Most important, it has been found that the actions of a given mediator may differ from setting to setting. Three factors are responsible for this variability (66):

1. *The state of activation of the target cell.* Interferon-γ, for example, prompts proliferation of quiescent fibroblasts but inhibits proliferation when fibroblasts are rapidly dividing (66). Prostaglandin E_2 stimulates release of TNFα from resting monocytes (110) but it inhibits TNFα production once the macrophages are activated (119).

2. *The nearby presence of other mediators.* Administration of TNFα cannot mimic the effects of endotoxic shock unless PAF is present (120, 121). Neutrophil generation of superoxide anions can be attenuated in the presence of platelets but not in platelet-free environments (122).

3. *The ability of the target cell to release other mediators.* Tumor necrosis factor α and interleukin-1 each cause fibroblast proliferation, but the combination of the two synergistically produces PGE_2 release, which, in turn, blocks fibroblast proliferation (66). Endothelial cells can lose their ability to secrete EDRF following exposure to endotoxin (41); secretion is als altered by shear stress and changes in wall tension (123). Surface

expression of adhesion molecules is both site-specific and time-dependent (53, 124).

Other Variables

Three other variables must be considered in any discussion of the role of these mediators in sepsis: the clinical status of the patient before the onset of sepsis, the length of time the patient has been ill, and innate variations in patients' ability to secrete these mediators.

Severe sepsis and septic shock do not develop in healthy persons; in most instances, they develop in persons with preexisting severe disease or in persons who have suffered catastrophic acute illness or trauma. This point may seem obvious but should not be overlooked. Patients at greatest risk of dying of sepsis are the elderly; those receiving immunosuppressive drugs; and those with malignancies, cirrhosis, asplenia, or multiple underlying disorders (such as diabetes mellitus, renal failure, or heart disease). As described above, however, these patients often already have elevated levels of one or more inflammatory mediators. They may also have activated macrophages, neutrophils, and T cells, and thus are "primed" for the release of additional mediators.

Production of other mediators, however, may sometimes be reduced in such patients. For example, vascular tissue is less able to generate PGI_2 in elderly patients, in patients with diabetes, and in patients with atherosclerosis (39); this decrease in PGI_2 generation may contribute to the loss of EDRF in these patients. Increased production of some mediators coupled with decreased production of others may make it difficult for the body to restore homeostasis.

The length of the patient's illness may also alter the "mix" of mediators. Synthesis of cytokines may be decreased after continued infection, downregulation of the relevant receptor may occur, or inhibitors may eventually be generated. This may help explain why high circulating levels of some mediators in a susceptible patient do not produce the massive toxic response that occurs in a healthy volunteer.

There may also be innate differences in patients' response to (or ability to produce) TNFα and other mediators. After injection of endotoxin, human subjects show marked variation in TNFα levels and response to fever (78, 125). The finding of increased cytokine levels in patients with various arthritides or inflammatory bowel disease further supports the concept that some patients may be inherently more susceptible to cytokine-induced damage.

Endothelial Dysfunction, Sepsis, and Septic Shock

How then do these mediators contribute to the development of sepsis? As noted above, sepsis usually begins with a nidus of infection or injury. At the site of original involvement, endotoxin, enterotoxin, or another stimulus prompts macrophages to release cytokines, PAF, eicosanoids, and T- and B-cell products. These products, however, are most likely to be found in the immediate microenvironment; they may be absent in other areas.

In the microenvironment, the beneficial effects of these mediators probably outweigh the negative effects; they enhance host defenses against infection and contribute to tissue remodeling (21). If the infection is not brought under control, however, one or more of these mediators—or endotoxin itself—may leak into the circulation.

Once in the circulation, endotoxin or TNFα (but probably many other mediators as well) is capable of triggering the full sepsis cascade. Whether this occurs depends on several factors, including the nearby presence or absence of other mediators released into or already present within the circulation, the nearby presence or absence of macrophages and activated neutrophils in the circulation, the relative health of the patient's vital organs (other than the infected organ or organs), and the underlying status of the patient's endothelium.

In the best clinical scenario, the release of endotoxin or mediator into the circulation will not cause sepsis. Built into the sepsis cascade are many places at which the system can downregulate itself. Oxidative products may provide negative feedback to control inflammation (110, 126, 127). Prostaglandin E_2 release may dampen the ability of macrophages to release cytokines and other mediators (128), and macrophages may be able to actively suppress T cells (129), thereby restoring homeostasis.

In some patients, unfortunately, downregulation does not occur; too much endotoxin or mediator may have been released, appropriate mediators to promote downregulation may not be present, or too many other mediators are released before downregulation begins. At this point, the patient will have begun to demonstrate clinical evidence of a systemic response to infection, thereby meeting the definition for sepsis presented in Table 1.

Inflammatory mediators will continue to circulate until they become inactive or until they reach the capillaries. In the capillaries, they may begin to cause endothelial damage through the mechanisms described above. Should sufficient damage be done to any one site, the patient will show signs of organ failure, thereby fulfilling the criteria for the sepsis syndrome.

The endothelium has an elaborate defense system. Like macrophages, endothelial cells are able to secrete TNFα, interleukin-1, interleukin-6, and PAF (99, 114, 115, 130), as well as the metabolites of arachidonic acid (38, 131-133) and also EDRF and endothelin-1 (39). Given the short half-lives of many of these mediators (thromboxane A_2 and PGI_2 have half-lives of about 30 seconds; EDRF, approximately 6 seconds), endothelial release of these substances may well be more important than macrophageal release in the pathogenesis of sepsis. Again, the initial effects of the mediators may be beneficial: Endothelial damage is repaired and the patient recovers.

If the endothelium cannot repair itself and additional mediators are released into the circulation, however, more sites of damage will develop. Ultimately, the blood pressure drops. The reason that hypotension occurs is not fully understood; it may result from the effects of many of these mediators (especially TNFα) on the heart, from the effects of a more specific mediator

(such as myocardial depressant substance), from the augmented release of EDRF or bradykinin, or from some combination of the above. Once hypotension develops, the patient fulfills the criteria for septic shock.

The sequence of events I have outlined can best be envisioned as a pyramid (Figure 2), in which each level reflects progressively greater degrees of endothelial damage. It is important to remember, however, that the same factors that contribute to endothelial damage in one organ may simultaneously or sequentially promote de-endothelialization elsewhere. Further, each site of inflammation may release yet more mediators into the circulation, thereby increasing the likelihood that additional damage will be done.

At each of these sites, a different mix of mediators may be responsible for endothelial destruction. In addition, the extent of damage may differ at each site. In some places, inflammation may be inhibited and homeostasis restored; in other places, endothelial destruction may continue unabated until organ failure ensues.

Implications

This model has important implications for diagnosis and therapy. First, the development of sepsis or its sequelae does not require the persistent release of endotoxin into the circulation; many of the mediators may initiate the process. This may help explain why many septic patients are never shown to be bacteremic. Second, as discussed, the amount of endotoxin or mediator released initially does not need to be large; small amounts of TNFα or PAF, for example, may be more than capable of causing sepsis in the setting of neutrophil activation and endothelial damage. Further, the continued presence of the instigating mediator is not required for sepsis to develop.

Once organ damage occurs, however, local release of mediators can be quite extensive. Bronchoalveolar lavage fluid specimens from patients with the adult respiratory distress syndrome, for example, have been shown to have TNFα concentrations greater than 500 U/mL (12 500 pg/mL) (134), a level dramatically higher than the highest serum levels detected in patients with septic shock.

Third, different mediators may be the initial stimulus in different patients. This theory may help explain why different organs are affected initially in different patients. For example, TNFα binds preferentially to the kidney, lung, and liver (135, 136); PAF often contributes to gastrointestinal ulceration (137); and the kidneys are more sensitive to the effects of endothelin-1 than are the other organs (138).

Fourth, if sufficient endothelial damage occurs, new organisms may be allowed into the bloodstream. This may occur most often in the gastrointestinal tract; bacterial translocation may promote the release of yet additional mediators. Extensive damage to any one organ will also hinder the body's ability to respond to ongoing infection. For example, damage to the pulmonary vasculature will alter the body's ability to remove endothelin-1 from the circulation (111). Alveolar macrophages have also been shown to gradually lose their ability to kill cell-associated *Staphylococcus aureus* and *Escherichia coli* (139). Hepatic damage may disrupt the reticuloendothelial system and limit the systemic response to sepsis (140).

Finally, any treatment plan for sepsis must take into account the fact that at any given time, a patient will have multiple, often persistent sites of inflammation, each at a different stage. Thus, by the time a patient has the sepsis syndrome or septic shock, monotherapy is unlikely to be effective. Most patients will require a host of treatments, and the earlier therapy is started, the more likely it will be effective.

What if treatment is not given in time? I believe that the sepsis cascade can eventually become self-perpetuating, independent of the original mediator or media-

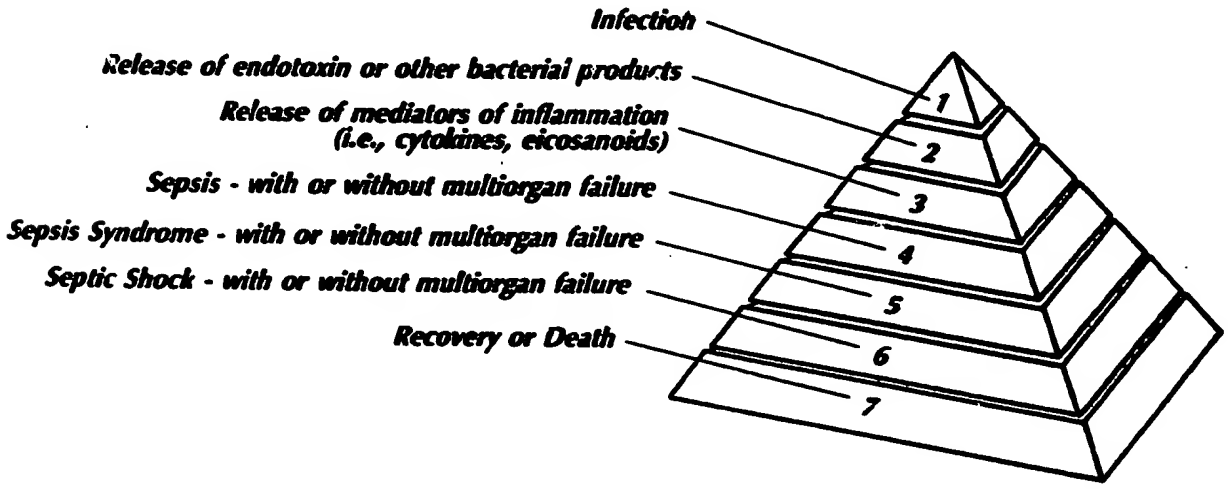

Figure 2. Model of sepsis. The mediators of sepsis can be shown to produce an expanding sequence of events according to the intensity or dose of the original insult. This is the model found in many experimental models of sepsis. The clinical syndrome of sepsis usually evolves over a longer time interval and causes a continuing insult. The systemic result is altered not only by the intensity of the response but by previous insults and earlier compensatory efforts (for example, the production of cytokine inhibitors or downregulators of relevant receptors). As a consequence, the inflammatory process is repeated at different sites; each site may be at a different stage of inflammation.

tors. Multiorgan failure ensues as m re and more sites of endothelial damage escape cc trol. The reticuloendothelial system eventually becomes hyperstimulated; macrophages l se the ability t secrete TNFα (18) and, possibly, interleukin-1 (141). The net result is a state f metabolic anarchy in which the body can no longer control what it has created. Unless effective treatment is given, too often the patient will die.

Appendix. Mediators of Endothelial Damage in Sepsis

Mediator	Major Reported Effects
Tumor necrosis factor α (TNFα)	Stimulates release of interleukin-1, interleukin-6, interleukin-8, platelet-activating factor, leukotrienes, thromboxane A_2, prostaglandins; may be able to stimulate macrophages directly to promote its own release
	Has only a weak effect on T cells
	Stimulates production of polymorphonuclear cells by bone marrow; enhances phagocytic activity of polymorphonuclear cells
	Promotes adhesion of endothelial cells, polymorphonuclear cells, eosinophils, basophils, monocytes, and, occasionally, lymphocytes by inducing increased expression of adhesion molecules
	Activates common pathway of coagulation and complement system
	Is directly toxic to vascular endothelial cells; increases microvascular permeability
	Produces a dose-dependent increase in endothelial procoagulant activity; may inhibit thrombomodulin expression at endothelial cell surface
	Suppresses lipoprotein lipase activity; inhibits acetate by adipocytes; decreases incorporation of glucose
	Stimulates collagenase release; has variable effects on fibroblast growth, depending on the presence of other mediators
	Reduces transmembrane potential of muscle cells and depresses cardiac myocyte shortening
	Induces class I histocompatibility molecules
	Acts directly on hypothalamus to produce fever
Interleukins	
Interleukin-1	Stimulates release of TNFα, interleukin-6, interleukin-8, platelet-activating factor, leukotrienes, thromboxane A_2, prostaglandins; may also be capable of stimulating its own production
	Activates resting T cells to produce lymphocytes and other products; supports B-cell proliferation and antibody production; is cytotoxic for insulin-producing B cells
	Promotes adhesion of endothelial cells, polymorphonuclear cells, eosinophils, basophils, monocytes, and, occasionally, lymphocytes by inducing increased expression of adhesion molecules
	Promotes polymorphonuclear cell activation and accumulation
	Increases endothelial procoagulant activity and endothelial release of plasminogen activator inhibitor
	Acts synergistically with TNFα; enhances tissue cell sensitivity to TNFα
	Suppresses lipoprotein lipase activity
	Encourages collagenase release from synovial cells; affects fibroblast proliferation and stimulation of its secretory products
	Promotes release of adrenocorticotropic hormone
	Acts directly on hypothalamus to produce fever
Interleukin-2	May promote release of TNFα and interferon-γ
	Required for proliferation of activated T cells
	Decreases arterial pressure, systemic vascular resistance, and ejection fraction; increases cardiac output
Interleukin-4	Enhances lymphocyte adhesion to endothelial cells
	Regulates growth or differentiation of hematopoietic factors, including T cells and mast cells
	Induces antigen expression on macrophages
	Suppresses interleukin-8 expression from stimulated monocytes but not from stimulated fibroblasts or endothelial cells
	Synergistically increases TNFα- or interleukin-1-induced antigen expression on endothelial cells, but inhibits the increased expression of adhesion molecules by TNFα, interleukin-1, or interferon-γ
Interleukin-6	Acts as a helper cell for T- and B-cell activation; interacts synergistically with interleukin-1 to affect thymocyte proliferation; in combination with TNFα, augments T-cell proliferation
	Promotes polymorphonuclear cell activation and accumulation
Interleukin-8	Is chemotactic for both neutrophils and lymphocytes; induces tissue infiltration of both
	Inhibits endothelial-leukocyte adhesion; decreases the hyperadhesion induced by those molecules
Platelet-activating factor	Stimulates release of TNFα, leukotrienes, thromboxane A_2
	Promotes leukocyte activation and subsequent free-radical formation
	Encourages platelet aggregation leading to thrombosis
	Markedly alters microvascular permeability, thereby promoting microvascular fluid loss
	Stimulates calcium influx-efflux in end thelial cells; causes such cells to retract and lose reciprocal contact (allowing exposure of the subintimal tissue t the blood stream), and promotes albumin diffusion in endothelial cells
	Exerts a negative inotropic effect n the heart; lowers arterial blood pressure
	May attenuate effects of endot xin on hyperglycemia and hyperlactacidemia
	May cause gastrointestinal ulceration, particularly in the duodenum and jejunum
	Induces blood-brain damage and vasoconstriction; may be neurotoxic

Appendix. Mediators of Endothelial Damage in Sepsis (Continued)

Mediator	Major Reported Effects
Leukotrienes	
Leukotriene B_4	Promotes neutrophil chemotaxis and adhesion of neutrophils to endothelium (neutrophils have specific receptors for leukotriene B_4) Is weakly chemotactic for eosinophils Increases vascular permeability, either directly or through interaction of neutrophils and endothelial cells
Leukotriene C_4, leukotriene D_4, and leukotriene E_4	Stimulate release of prostacyclin Increase vascular permeability directly by causing contraction of adjacent endothelial cells and a resulting increase in the diameter of interendothelial-cell pores Decrease coronary blood flow and myocardial contractility; increase pulmonary vascular resistance; decrease mesenteric blood flow but have no effect on renal blood flow Have mild vasoconstrictive effects themselves and enhance vasoconstrictive effects of epinephrine and norepinephrine; however, can relax precontracted arterial segments (only when endothelial lining is intact)
Thromboxane A_2	Promotes release of endothelium-derived relaxing factor; may stimulate prostacyclin production Causes platelet aggregation and neutrophil accumulation Increases vascular permeability; enhances permeability of both single- and double-unit membranes Produces vasoconstriction of vascular beds and pulmonary bronchoconstriction
Prostaglandins	
Prostaglandin E_2	Inhibits both interleukin-1 production and the responsiveness of thymocytes to interleukin-1 Low concentrations stimulate TNFα release; higher concentrations suppress TNFα production at a dose-dependent level Inhibits mitogenesis of T and B cells Causes vasodilation and increased blood flow Has a beneficial effect on tissue perfusion and may thereby decrease the severity of tissue damage Acts synergistically with prostacyclin to increase the effects of serotonin and bradykinin on vascular permeability Promotes muscle catabolism Inhibits (at a dose-dependent level) endotoxin's ability to produce hypotension and gastric damage Increases intracellular cyclic AMP levels Acts directly on hypothalamus to produce fever
Prostacyclin (Prostaglandin I_2)	Inhibits platelet aggregation and adhesion (this effect may be synergistically increased by endothelium-derived relaxing factor) Inhibits thrombus formation; may have fibrinolytic activity Acts synergistically with prostaglandin E_2 to increase the effects of serotonin and bradykinin on vascular permeability Causes vasodilation and increased blood flow In the early stages of sepsis, exerts a beneficial effect on tissue perfusion Produces smooth muscle relaxation
Interferon-γ	Promotes release of TNFα, interleukin-1, interleukin-6 (possibly due to its ability to augment effects of endotoxin on macrophages); augments production of adhesion molecules May act synergistically with TNFα to produce cytotoxic and cytostatic activity; interacts with other cytokines in variable ways Synergistically increases interleukin-2 promotion of TNFα release Helps activate B cells to increase antibody production Enhances adhesion of lymphocytes to endothelial cells Produces marked morphologic changes in endothelial cells Encourages polymorphonuclear cell activation and accumulation; enhances the phagocytic activity of polymorphonuclear cells Promotes macrophage activation, macrophage microbicidal function, and expression of cellular receptors for TNFα Induces class I and class II histocompatibility molecules May antagonize production of granulocyte-monocyte colony-stimulating factor Acts directly on hypothalamus to produce fever
Granulocyte-monocyte colony-stimulating factor	Stimulates polymorphonuclear cell phagocytosis, degranulation, and cytotoxicity Promotes macrophage maturity and enhances macrophage activity
Endothelium-derived relaxing factor	Relaxes vascular smooth muscle Inhibits platelet aggregation and adhesion (this effect may be synergistically increased by prostacyclin) Inhibits mitogenesis in vascular smooth muscle cells
Endothelin 1	Strongly promotes vasoconstriction By increasing glomerular resistance, may cause renal hypoperfusion and hypofiltration Promotes release of endothelium-derived relaxing factor and prostacyclin Encourages mitogenesis in vascular smooth muscle cells

(Continued on next page)

Appendix. Mediators of Endothelial Damage in Sepsis (Continued)

Mediator	Major Reported Effects
Complement fragment $C3_a$	Causes mast cells to degranulate and release vasodilat ry mediators May promote end toxin-stimulated release of thromboxane A_2 and prostacyclin Causes smooth muscle contraction and mucus secretion
Complement fragment $C5_a$	Causes mast cells to degranulate and release vasodilatory mediators May promote endotoxin-stimulated release of thromboxane A_2 and prostacyclin Promotes TNFα release Enhances polymorphonuclear cell activation, migration, adherence, and aggregation Induces capillary leakage May depress systemic vascular resistance and produce hypotension
Polymorphonuclear cells	Can release directly, or indirectly promote release of, most of the mediators described above Have variable effects on platelet aggregation During degranulation, release free-oxygen species and lysosomal enzymes, which, in turn, may: A. Damage vascular endothelium, mitochondria, and collagen B. Cause polymorphonuclear cell dysfunction, erythrocyte fragility, intravascular hemolysis, and vascular smooth muscle contraction C. Enhance smooth muscle sensitivity to alpha-adrenergic agonists D. Counteract the effects of endothelium-derived relaxing factor During aggregation: A. Create microemboli, which contribute to arteriole occlusion and gross peripheral maldistribution of blood flow During adherence to endothelial wall: A. Produce a variable effect on tone in vessels with intact endothelium, depending on concentration B. Produce dose-dependent smooth muscle relaxation in de-endothelialized vessels C. Release endothelium-derived relaxing factor-like substance called neutrophil-derived relaxing factor D. Migrate through interendothelial cell junctions and accumulate in subcellular regions
Adhesion molecules	Act as ligands for receptors on inflammatory cells
Endothelial-leukocyte adhesion molecule-1	Attracts neutrophils to vascular endothelium
Intercellular adhesion molecule-1	Attracts neutrophils and B lymphocytes (but not T lymphocytes) to vascular endothelium Helps neutrophils and T lymphocytes to transmigrate across endothelial monolayers
Vascular cell adhesion molecule-1	Mediates binding of monocytes and lymphocytes to vascular endothelium
Platelets	Promote release of endothelium-derived relaxing factor, prostacyclin Produce transforming growth factor-β_1, serotonin, thromboxane A_2; also release 12-hydroxy acids that are metabolized by neutrophils into leukotriene B_4 Induce vasoconstriction and stimulate neutrophils (both effects require release of other mediators)
Transforming growth factor β_1	Recruits macrophages to area of injury, then stimulates them to release interleukin-1 and more transforming growth factor-β_1 May suppress macrophages' ability to release reactive oxygen species and to promote leukocyte adherence to endothelium May suppress TNFα-induced inflammation Promotes cell growth, repair, metabolism; increases production of extracellular matrix by mesenchymal cells Causes intestinal smooth muscle cells to double collagen production but has no effect on cell proliferation
Bradykinin	Promotes release of endothelium-derived relaxing factor, prostacyclin
Thrombin	Stimulates release of platelet-activating factor from human endothelial cells; disrupts platelet-activating factor regulation Promotes release of endothelium-derived relaxing factor (this may decrease with age) and prostacyclin; also encourages endothelin-1 release Mediates the activation of interleukin-8 in the procoagulant environment associated with endothelial cells Encourages fibrinogen consumption and pulmonary vasoconstriction Protein C activator (a derivative of thrombin) inactivates coagulation factors V_a and $VIII_a$

(*Continued on next page*)

Appendix. Mediators of Endothelial Damage in Sepsis (Continued)

Mediator	Major Reported Effects
Myocardial depressant substance	Produces reversible myocardial depressi n, ventricular dilation, decreased left ventricular ejection fraction May cause ventricular diastolic pressure abnormalities Does not seem to affect afterload r heart rate
β-End rphin	May contribute to glucose-mediated hyperinsulinism May cause hypotension
Heat shock proteins	Prevent and repair cellular injury after hyperthermia and oxidative stress Induce tolerance to subsequent stress Cannot be induced during endotoxin challenge

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